TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER 0480/001178

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP 98/06545	15 October 1998	23 October 1997

TITLE OF INVENTION: THE USE OF TNF ANTAGONISTS AS DRUGS FOR TREATING SEPTIC DISORDERS

APPLICANT(S) FOR DO/EO/US Hartmut KUPPER, Martin KAUL, Juergen EISELSTEIN, Lothar DAUM Joachim KEMPENI

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. /X/ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.

2. / / This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.

3. /X/ This express request to begin national examination procedures (35 U.S.C.371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. /X / A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. /X/ A copy of the International Application as filed (35 U.S.C. 371(c)(2)).

   a./X/ is transmitted herewith (required only if not transmitted by the International Bureau).
   b./ / has been transmitted by the International Bureau.

   c./ / is not required, as the application was filed in the United States Receiving Office (RO/US0).

6. /X/ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. / / Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).

   a./ / are transmitted herewith (required only if not transmitted by the International Bureau).
   b./ / have been transmitted by the International Bureau.
   c./ / have not been made; however, the time limit for making such amendments has NOT expired.
   d./ / have not been made and will not be made.

8. / / A translation of the amendments to the claims under PCT Article 19(35 U.S.C. 371(c)(3)).

9. /X/ An oath or declaration of the inventor(s)(35 U.S.C. 171(c)(4)).

10./ / A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11./X/ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12./X/ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13./ / A FIRST preliminary amendment.
/ / A SECOND or SUBSEQUENT preliminary amendment.

14./ / A substitute specification.

15./ / A change of power of attorney and/or address letter.

16./X/ Other items or information.
International Search Report
International Preliminary Examination Report

09/529795

422 Rec'd PCT/PTO 20 APR 2000

U.S. Appln. No. (If Known) | INTERNATIONAL APPLN. NO. PCT/EP 98/06545 | ATTORNEY'S DOCKET NO. 0480/001178

17. /X/ The following fees are submitted	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO.....$840.00	840.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482).....$750.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....$700.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $970.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....$98.00		
ENTER APPROPRIATE BASIC FEE AMOUNT = $	840.00	
Surcharge of $130.00 for furnishing the oath or declaration later than / / 20 / /30 months from the earliest claimed priority date (37 CFR 1.492(e)).		

Claims	Number Filed	Number Extra	Rate	
Total Claims	7	-20	X$18.	
Indep.Claims	3	-3	X$78.	
Multiple dependent claim(s)(if applicable)			+260.	
TOTAL OF ABOVE CALCULATION			=	840.00
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				
SUBTOTAL			=	**840.00**
Processing fee of $130. for furnishing the English translation later than / /20 / /30 months from the earliest claimed priority date (37 CFR 1.492(f)).			+	
TOTAL NATIONAL FEE			=	840.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) $40.00 per property			=	40.0
TOTAL FEES ENCLOSED			= $	**880.00**
Amount to be refunded:			$	
Charged			$	

a./X/ A check in the amount of $ 880.00 to cover the above fees is enclosed.

b./ / Please charge my Deposit Account No._____in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c./X/ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **11-0345**. A duplicate copy of this sheet is enclosed.

+

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.

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1/PRT

The use of TNF antagonists as drugs for treating septic disorders

The present invention relates to the use of TNF antagonists for treating septic disorders.

It is known that the term tumor necrosis factor (TNF) embraces two cytotoxic factors (TNF-α and TNF-β) which are mostly produced by activated lymphocytes and monocytes.

EP 260 610 describes, for example, anti-TNF antibodies which are said to be usable for inactivating TNF in disorders associated with an increase in TNF in the blood, such as septic shock, transplant rejection, allergies, autoimmune diseases, shock lung, coagulation disturbances or inflammatory bone disorders.

In medical textbooks, septic disorders are defined as a collective term for clinical states in which agents causing inflammation, eg. bacteria, start from a focus and reach the blood stream, which initiates a wide range of subjective and objective pathological manifestations. It is further found that the clinical picture may vary widely depending on the type of causative agent, the responsivity of the body, the primary focus and the varying involvement of organs (Sturm et al. "Grundbegriffe der Inneren Medizin", 13th Edition, page 570, Gustav Fischer Verlag, Stuttgart, 1984).

A number of cytokines have been suggested to be involved in the complex pathophysiological process of sepsis. TNF in particular is, on the basis of data from animal experiments (Beutler et al., Science 229 (1985) 869-871), ascribed an important role in septic shock.

This eventually led to clinical studies being carried out on the treatment of sepsis patients with anti-TNF antibodies.

However, it was found in a recently published multicenter phase II study on the treatment of severe sepsis with a murine monoclonal anti-TNF antibody that the overall group (80 patients) did not benefit in terms of survival rate from the treatment with the antibody. Only the patients with elevated TNF concentrations in the circulation appeared to benefit in terms of the probability of survival from high-dose anti-TNF antibody administration (C.J. Fisher et al., Critical Care Medicine, Vol.

21, No.3, pages 318-327). There is also a reference in this study to a correlation between the plasma levels of TNF and IL-6.

The part played by the cytokine interleukin-6 (IL-6) in sepsis is unclear and contradictory. Elevated levels of IL-6 have been found in the serum of some sepsis patients (Hack et al., Blood 74, No. 5, (1989) 1704-1710).

Waage describes a correlation between the concentrations of the cytokines IL-6 and IL-8 and the severity of the shock, but they have no effect, either alone or in combination with TNF, in terms of mortality, on the development of a shock syndrome (Waage in "Tumor Necrosis Factors", ed. B. Beutler, Raven Press, New York, 1992, pages 275-283).

Some scientists have ascribed a beneficial role to IL-6 in septic shock because IL-6 inhibits, in the form of negative feedback control, the LPS-induced TNF production (Libert et al. in "Tumor Necrosis Factor: Molecular and Cellular Biology and Clinical Relevance", ed. W. Fiers, Karger, Basle, 1993, pages 126-131).

WO 95/00291 discloses TNF antagonists as medicines for treating sepsis in patients in whom the serum levels of interleukin-6 are 500 pg/ml or more.

However, it emerged from clinical studies that the treatment disclosed in WO 95/00291 was not always successful.

It is evident that there are cases of sepsis which can be treated successfully with TNF antagonists, while in other cases treatment with TNF antagonists is not successful and is in fact contraindicated.

It is an object of the present invention to identify, reliably and rapidly, those patients suffering from sepsis who can be successfully treated with TNF antagonists.

We have found that this object is achieved by using the following features to identify patients with septic disorders who can be treated successfully:

The serum level of interleukin-6 is increasing, ie. within a measurement period of at least 30 minutes the level measured at the later time is higher than the level measured first.

Patients suffering from sepsis and satisfying this criterion are very suitable for treatment with TNF antagonists.

The treatment is preferably carried out on patients whose serum level of interleukin-6 in the measurement period is at least 500 pg/ml. However, it may also be distinctly higher than this level and be up to the order of a few mg/ml.

In order to establish whether the serum level of interleukin-6 (IL-6) is increasing, it is necessary to carry out at least two IL-6 measurements.

The second, later measurement should be obtained within a period of from 30 minutes to 48 hours after the first IL-6 measurement (measurement period).

The measurement period is preferably 2 - 24, in particular 4 - 10, hours.

The patients to be treated are, as a rule, undergoing intensive medical treatment which sometimes does not permit strict measurement period limits to be complied with.

The extent of the rise in the serum level of IL-6 between the two measurements is not so crucial for the use according to the invention.

If the serum level of IL-6 does not increase or even falls during the measurement period, treatment with TNF antagonists is not recommended.

The serum concentrations of IL-6 can be determined by conventional detection methods such as RIA or ELISA. An example of a very suitable detection system is the IL-6-EASIA supplied by Medgenix.

The concentration of IL-6 can also be determined in an activity assay in which, for example, C-reactive protein is assayed.

Since different measurement methods or assay systems sometimes give different results for the same measurement, it is advisable either to use the same measurement method or assay system for

determining the IL-6 levels or, if different systems are used, to calibrate them against each other.

Suitable TNF antagonists are anti-TNF antibodies, TNF receptors or soluble fragments thereof, TNF-binding proteins or those TNF derivatives which still possess TNF receptor binding but no longer have any TNF activity. TNF antagonists of these types have the characteristic that they trap TNF which has already been produced and do not allow it to reach the TNF receptor or that they compete with the TNF for the receptor.

However, TNF antagonists which prevent the formation or release of TNF are also suitable for the use according to the invention. Substances of this type inhibit, for example, TNF gene expression or the release of TNF from precursor forms. Examples of suitable TNF antagonists are inhibitors of TNF convertase.

TNF-antagonistic activities have been described, for example, for xanthine derivatives, glucocorticoids, prostaglandin E 2, thalidomide, interleukin-4, interleukin-10, granulocyte stimulating factor (G-CSF), cyclosporin and α-antitrypsin. Thus compounds of these types are also suitable as TNF antagonists.

The TNF antagonists suitable for the use according to the invention are described, for example, by Mariott et al. DDT, Vol. 2, No. 7, July 1997 and in the literature cited therein.

Anti-TNF antibodies and fragments thereof are particularly preferred for the use according to the invention.

The anti-TNF antibodies suitable for the use according to the invention are known (EP 260 610, EP 351 789, EP 218 868). It is possible to use both polyclonal and monoclonal antibodies. Also suitable in addition are TNF-binding antibody fragments such as Fab or $F(ab')_2$ fragments or single-chain Fv fragments.

Humanized or human anti-TNF antibodies or their TNF-binding fragments are also very suitable because these molecules ought not to cause any anti-mouse antigenicity in human patients.

It is also possible to use mixtures of various anti-TNF antibodies or of anti-TNF antibodies and TNF receptor fragments as active ingredient.

The present invention includes pharmaceutical compositions which, besides nontoxic, inert pharmaceutically suitable carriers, comprise the anti-TNF antibodies, and processes for producing these compositions.

The anti-TNF antibodies are formulated in a way customary for biotechnologically produced active ingredients, as a rule as liquid formulation or lyophilisate (see, for example, Hagers Handbuch der pharmazeutischen Praxis, Vol. 2, 5th Edition, 1991, page 720, ISBN 3-540-52459-2). The pharmaceutical compositions mentioned above are produced in a conventional way by known methods, for example by mixing the active ingredient(s) with the carrier(s).

It has in general proven advantageous to administer the active ingredient(s) suitable for the use according to the invention in total amounts of about 0.1 to about 100, preferably 0.1 to 10, mg/kg of body weight every 24 hours, where appropriate in the form of several individual doses or as continuous infusion and, where appropriate, over a treatment period of several days to achieve the desired results. Administration can take place as brief intravenous infusion of the single doses or as continuous long-term infusion of the daily dose over 24 hours. A single dose preferably contains the active ingredient(s) in amounts of about 0.1 to about 10 mg/kg of body weight. However, it may be necessary to deviate from the stated dosages, in particular as a function of the age and size of the patient to be treated and the nature and severity of the underlying disorder, the nature of the composition and of the administration of the drug, and the period over which administration takes place.

The invention is illustrated further in the following example.

Example

Treatment of sepsis patients with a murine anti-TNF antibody fragment ($F(ab')_2$), called MAb 195F (INN: AFELIMOMAB).

In total, 251 patients with severe sepsis who where treated either with an anti-TNF antibody fragment (afelimomab) or as control patients were analyzed in a multicenter clinical study.

Of the 251 patients, 47 had an increasing and 178 had a decreasing serum level of IL-6.

The figure shows that a decrease in mortality can be achieved by the treatment in the group with increasing IL-6 level (55.6% mortality compared with 69% in the controls).

There is no evident success of treatment with MAb 195 F in the group where the serum level of IL-6 was falling; on the contrary, in fact an adverse effect of the treatment is evident (mortality 54.7% compared with 50.6% in the control group).

The treatment group received, in addition to the standard treatment of sepsis, the trial product afelimomab over a period of 3 days as a total of nine brief infusions lasting 15 minutes, each at intervals of eight hours, in a single dose of 1 mg/kg of body weight each time. The control group received in addition to the standard treatment of sepsis a pharmacologically inactive sham product (placebo) administered in the same regimen.

The result of this clinical study clearly demonstrates that the treatment of severe sepsis with anti-TNF antibodies is particularly successful when the sepsis patients who are treated have an increasing serum level of IL-6. Patients who have a falling serum level of IL-6 should accordingly not be treated with TNF antagonists.

We claim:

1. The use of TNF antagonists for producing drugs for treating those septic disorders where the serum level of interleukin-6 increases in a measurement period of at least thirty minutes.

2. The use as claimed in claim 1, wherein the serum level of interleukin-6 is 500 pg/ml and above in the measurement period.

3. The use as claimed in claim 1, wherein the measurement period is 4 - 10 hours.

4. The use as claimed in claim 1, wherein an $F(ab')_2$ fragment of a monoclonal anti-TNF antibody is used as TNF antagonist.

5. A commercial pack comprising a TNF antagonist together with instructions for the use of this TNF antagonist for treating septic disorders where the serum level of IL-6 increases in a measurement period of at least thirty minutes.

6. A commercial pack as claimed in claim 5, wherein a monoclonal anti-TNF antibody is used as TNF antagonist.

7. A method for establishing whether a patient suffering from sepsis is to be treated with TNF antagonists, which comprises the following steps:

   (a) determination of the serum level of interleukin-6 in the patient at a first time t_1

   (b) determination of the serum level of interleukin-6 at a second time t_2 which is at least 30 minutes after the first time t_1, and determination of the ratio

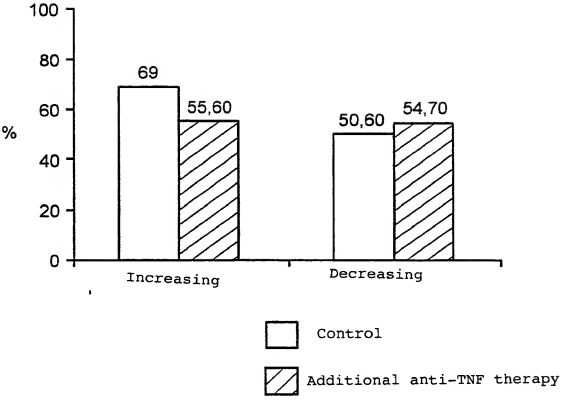
$$V = \frac{\text{IL-6 level } (t_2)}{\text{IL-6 level } (t_1)}$$

   (c) treatment with TNF antagonists in the case where $V > 1$.

The use of TNF antagonists as drugs for treating septic disorders

Abstract

TNF antagonists are used to produce drugs for treating septic disorders where the serum level of interleukin-6 increases in a measurement period of at least thirty minutes.


100
80
60
40
20
0
%
69
55,60
50,60
54,70
Increasing
Decreasing
Control
Additional anti-TNF therapy

Declaration, Power of Attorney

0480/001178

We (I), the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

The use of TNF antagonists as drugs for treating septic disorders

the specification of which

[ ] is attached hereto.

[ ] was filed on _____ as

Application Serial No. _____

and amended on _____.

[x] was filed as PCT international application

Number PCT/EP98/06545

on 15/10/1998

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above–identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)–(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	**Country**	**Day/Month/Year**	**Priority Claimed**	
19746868.3	*Germany*	*23 October 1997*	[x] Yes	[ ] No

We (I) hereby claim the benefit under Title 35, United States Codes, § 119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	**Filing Date**	**Status (pending, patented, abandoned)**

And we (I) hereby appoint **Messrs. HERBERT. B. KEIL**, Registration Number 18,967; and **RUSSEL E. WEINKAUF**, Registration Number 18, 495; the address of both being Messrs. Keil & Weinkauf, 1101 Connecticut Ave., N.W., Washington, D.C. 20036 (telephone 202–659–0100), our attorneys, with full power of substitution and revocation, to prosecute this application, to make alterations and amendments therein, to sign the drawings, to receive the patent, and to transact all business in the Patent Office connected therewith.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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